overcome the 35 U.S.C. §102 rejections based on cited prior art, or in an effort to overcome rejections based on 35 U.S.C. § 112. The new claims 100-139, and 143-150 are fully supported by the specification as originally filed, and lie within the scope of claims already in prosecution. Support for newly added claim 140-142, and 151 can be found in the originally filed specification at, for example, page 8, first full paragraph, page 23, first full paragraph, and page 56, first full paragraph.

Thus, no new matter has been added by way of amendments to the specification or the claims.

I. Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejects claims 37-40 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinate.

The Examiner contends "[i]t is unclear whether applicant intends the term 'm-371' to designate a range, i.e., from integer m **to** 371, or if the applicant intends the term to designate an arithmetic expression, i.e., interger m **minus** 371." (*See, e.g.,* Paper 11, Page 4, Paragraph 7.)

Although Applicants disagree that the claim as written is indefinite, Applicants have adopted the Examiner's suggestion.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

II. Rejections Under 35 U.S.C. § 102

The Examiner rejected claims 37 and 38 under 35 U.S.C. § 102(b) as allegedly being anticipated by GenEmbl accession number X91553.

Applicants respectfully disagree with the rejection over GenEmbl accession number X91553. However, in the interest of facilitating prosecution, Applicants have amended section (c) of claim 37 to recite "wherein said polynucleotide is not Genbank Accession No. X91553." Support for this language can be found in the instant specification at page 23, lines 11-14.

Accordingly, Applicants believe the Examiner's concerns have been fully addressed and respectfully request reconsideration and withdrawal of the rejection of claims 37 and 38 under 35 U.S.C. § 102(b).

III. Rejections Under 35 U.S.C. §101 and §112, First Paragraph

The Examiner rejected claims 25-99 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific and substantial asserted utility or a well-established utility.

More specifically, the Examiner contends:

> [c]laims 25-99 are directed to polynucleotides of SEQ ID NO:1 encoding a polypeptide of SEQ ID NO:2. The instant specification puts forth that the polypeptide is useful in a method to determine what the physiological effects of the polypeptide might be (see page 55, beginning at line 31). This proposed use lacks a specific and substantial utility. It is not a specific use because any protein derived from natural sources could be used in exactly the same way. Further, many polynucleotides are known in the art to encode polypeptides, yet the polypeptides have no known function or known ligands. Any of these orphan clones could be used in the manner described in the specification for the claimed polynucleotide.

(See, Paper 11, Page 5-6, Paragraph 9.)

Applicants respectfully disagree and traverse.

A rejection under 35 U.S.C. § 101 is improper when a person of ordinary skill in the art would find credible disclosed features or characteristics of the invention, or statements made by the Applicant in the written description of the invention. *See* M.P.E.P. §§ 2107.01(II), (III) at 2100-[29-31] (Rev. 1, Feb. 2000). In addition, an Applicant need only make *one* credible assertion of utility for the claimed invention to satisfy 35 U.S.C. § 101. *See, e.g., Raytheon v. Roper,* 724 F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown."). *See,* M.P.E.P. at 2100-29. Finding a lack of utility is also improper if a person of ordinary skill in the art would know of a use for the claimed invention at the time the application was filed. M.P.E.P. § 2107.01(II)(B) at 2100-[29-30].

Contrary to the Examiner's comments, Applicants have set forth in the specification statements that clearly and fully describe the function of CRCGCL and explain why Applicants believe the invention is useful. For example, the specification explicitly teaches that CRCGCL has use, for example, as a cytokine receptor (*see, e.g.,* the instant specification at page 1, lines 8-9; page 7, line 35 through page 8, line 2; and page 8, lines 32-34) which activates the Jak-STAT signal transduction pathway (*see, e.g.,* the specification at page 1, line

29 through page 2, line 2; page 7, line 32, and Example 13 at pages 85-88, particularly page 85, lines 32-34 and page 86, line 1), thereby regulating the differentiation and/or proliferation of immune cells (*see, e.g.,* page 56, lines 3 to 8 and lines 19-21). Thus, the specification clearly teaches a specific and substantial assertion of utility of the disclosed polynucleotides (and the encoded polypeptides) as involved in immune cell regulation. The biological role and significance of CRCGCL polynucleotides (and the encoded polypeptides), as well as its specific and substantial utility, are clearly taught by the specification as originally filed. Applicants assert that such characterization is sufficient on its own to constitute a showing of utility.

Moreover, although not required to satisfy the requirements of 35 U.S.C. §§ 101 and 112, Applicants provide the Declaration of Paul Moore Under 37 C.F.R. § 1.132 which describes data from experiments performed at HGS which affirms the predicted use of CRCGCL in immune cell regulation by binding a cytokine and activating the Jak-STAT signal transduction pathway. A 293T reconstitution cell assay was used to assess whether CRCGCL polypeptides activate the Jak-STAT pathway (as measured by tyrosine phosphorylation), as has been shown for the IL-2R common gamma chain. Increased phosphorylation of STAT5 and Tyk2 was detected using this assay when CRCGCL was cotransfected with IL-7R alpha chain, Jak2, and STAT5 and stimulated with a cytokine, TSLP. The increased phosphorylation of STAT5 and Tyk2 could be inhibited by the addition of a CRCGCL fragment such as the soluble extracellular domain of CRCGCL. The results of these experiments indicate that (1) CRCGCL binds a cytokine and activates the Jak-STAT signal transduction pathway, and (2) the soluble extracellular domain of CRCGCL binds a cytokine and inhibits the Jak-STAT signal transduction pathway.

In addition, flow cytometry was used to measure whether CRCGCL polypeptides bind a cytokine. FACScan analyses were performed on 293T cells which had been transfected with either CRCGCL, IL-7R alpha chain, or IL-2R common gamma chain alone, or in combination with one another, and treated with a FLAG-tagged TSLP molecule bound to an anti-FLAG biotin conjugate and fluorescein isothiocyanate labeled streptavadin. A shift in the mean fluorescent intensity as measured by FACScan was detected when comparing 293T cells transfected with CRCGCL alone and in combination with IL-7R alpha chain treated with the FLAG-tagged TSLP to the same cells untreated. The results of these experiments indicate that CRCGCL binds a cytokine.

These results demonstrate that, as asserted in the specification as originally filed, CRCGCL binds cytokine and activates the Jak-STAT signal transduction pathway. Furthermore, the specification teaches that activation of the Jak-STAT pathway is indicative of proteins involved in cell proliferation, and in this case, immune cells (*see, e.g.,* the specification at page 8, lines 32-36; and page 85, lines 32-34). Applicants submit that it was well-known in the art at the time the present application was filed, and the specification further teaches explicitly that "there is a need for polypeptides that regulate the differentiation and proliferation of cells, since disturbances of such regulation may be involved in disorders relating to immune system." *See*, specification, at page 2, lines 9-11. Accordingly, Applicants have contemplated and disclosed many therapeutic applications of CRCGCL, for example, treatment of various immune system-related disorders, including, but not limited to, immunologic deficiency syndromes, autoimmune disorders, allergic reactions and conditions, graft-versus-host disease, and/or inflammation, consistent with the biological activity of CRCGCL. *See, e.g.*, specification, at page 56 line 18 through page 58, line 3.

In addition, Applicants have contemplated and disclosed the therapeutic use of fragments of CRCGCL to treat disease by inhibiting the action of CRCGCL (*see, e.g.,* specification at page 45, lines 24-25; page 62, lines 3-14 and line 37 through page 63, line 2). The experimental results described above which illustrate the ability of fragments of CRCGCL to bind a cytokine and inhibit the Jak-STAT signal transduction pathway confirm this asserted use.

Applicants submit that the above asserted utilities for CRCGCL are specific (the vast majority of proteins do not bind cytokine, activate a Jaks-STAT signal transduction pathway or modulate immune cell proliferation) and substantial ("the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." (Revised Interim Utility Guidelines Training Materials, p. 6)). In addition, Applicants submit that these utilities are credible.

With regard to these asserted therapeutic activities, Applicants note that there is no need to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. M.P.E.P. § 2107.02 (I) at 2100-[33-34]. All that is required of Applicants is that there be a reasonable correlation between the biological activity and the asserted utility. *See, Nelson v. Bowler*, 626 F.2d 853, 857 (C.C.P.A. 1980). Moreover, "[u]sefulness in patent law, and in particular in the context

of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana, 51* F.3d *1560, 1568* (Fed. Cir. 1995) (emphasis added).

Even assuming, *arguendo*, the Examiner has established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by proffering sufficient evidence to lead one skilled in the art to conclude that the asserted utilities are more likely than not true. Applicants have directed the Examiner to the specification where clear and specific assertions are made of CRCGCL biological and therapeutic activity and provided experimental evidence confirming the asserted utilities.

In view of the above, Applicants submit that the asserted utilities of the invention meet the statutory requirement set forth in 35 U.S.C. § 101. The Examiner has failed to establish and maintain grounds as to why a rejection for lack of utility is proper. Accordingly, Applicants respectfully request that the rejection be withdrawn.

The Examiner has also rejected claims 25-60 under 35 U.S.C. §112, first paragraph. In particular, the Examiner contends that "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility," one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation. (*See, e.g.*, Paper 11, Page 7, Paragraph 10.)

Applicants respectfully disagree and traverse.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, Applicants submit that the claimed invention is supported by a specific and substantial or well-established utility. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107(IV) at 2100-28 (Rev.1, Feb. 2000). Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of claims under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

IV. Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner further rejects claims 25-60 under 35 U.S.C. §112, first paragraph, for enablement.

More specifically, the Examiner alleges that:

> the claims encompass polypeptide variants of the polypeptide of SEQ ID NO:2, i.e., substitutions, deletions or insertions in a protein corresponding to SEQ ID NO:2; should Applicant establish a specific and substantial utility for the claimed polynucleotides, Applicant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO:2, but which still retain a desired property of the polypeptide of SEQ ID NO:2.

(See, Paper 11, Pages 7-8, Paragraph 10.)

Applicants respectfully disagree and traverse.

Preliminarily, Applicants point out that in order to enable the claimed invention as required by 35 U.S.C. § 112, the specification need only enable a person of ordinary skill in the art to make the polypeptides encoded by the claimed polynucleotides and practice a single use thereof without undue experimentation.[1] Thus, Applicants submit that to be fully enabled, the polypeptides of the invention encoded by the claimed polynucleotides need merely have application in a single use, such as, for example, to bind cytokine, activate the Jak-STAT signal transduction pathway, and modulate immune cell proliferation and/or differentiation. Because the CRCGCL polypeptide of the invention has a credible, specific and substantial use, antibodies raised against the CRCGCL polypeptide also have utility.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 USPQ 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely

---

[1] The Applicant need show utility for only one disclosed purpose. See *Raytheon Co. v. Roper Corp.*, 220 USPQ 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 USPQ 223 (Pat. Off. Bd. App. 1958).

quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

Furthermore, "[t]here is no magical relation between the number of representative examples and the breadth of the claims" with respect to enablement. *In re Borkowski*, 164 USPQ 642, 646 (C.C.P.A. 1970). The issue is not whether the specification discloses any or all alterations that can be made in the polypeptides encoded by the claimed polynucleotides, but rather whether polypeptides encoded by the polynucleotides encompassed by the claims have at least a single use, and this use can be confirmed, without undue experimentation, by following procedures either described in the specification or otherwise known in the art. See *In re Angstadt*, 190 USPQ 214, 218 (C.C.P.A. 1976):

> To require such a complete disclosure would apparently necessitate a patent with "thousands of examples . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments . . .

While the predictability of the *art* can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the *result* of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is <u>not</u> a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 USPQ 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, <u>with reasonable certainty before performing the reaction</u> whether the claimed product will be obtained, . . . then <u>all</u> "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is <u>uncertain</u>. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original). As Judge Rich explained in *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed.Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to *determine*, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed

utility" (emphasis provided). Since the disclosed or otherwise known methods of making and screening polypeptides (and fragments or variants thereof) encoded by the claimed polynucleotides may be used to make and then *determine*, without undue experimentation, whether a given polypeptide encoded by a polynucleotide encompassed by the claims is able to, for example, bind a cytokine, activate the Jak-STAT signal transduction pathway, modulate immune cell proliferation and/or generate CRCGCL specific antibodies and therefore possesses the disclosed utility, the enablement requirement is fully satisfied. *In re Wands*, 8 USPQ2d at 1404; *Ex parte Mark*, 12 USPQ2d 1904, 1906-1907 (B.P.A.I. 1989).

Applicants submit that the specification provides ample guidance for one of ordinary skill in the art to routinely make and use the polypeptides encoded by the claimed polynucleotides of the present invention. For example, the specification discloses both the nucleic acid and amino acid sequences of CRCGCL (SEQ ID NOS: 1 and 2, respectively), routine cloning methods (*see, e.g.*, Sambrook et al. cited on page 52, lines 30-31; page 70, line 20 through page 72, line 26; and page 74, line 8 through page 81, line 8), CRCGCL activity (*see, e.g.*, page 1, lines 8-9; page 8, lines 24-26; page 56, lines 3-8 and lines 19-21; page 85, lines 32-34 and page 86, line 1) and biological assays including, for example, assays to determine if a protein activates the Jak-STAT pathway (*see, e.g.*, pages 85-88, Example 13).

Moreover, the skill in the art of molecular biology is high. At the time of filing of the instant application, assays to measure cytokine binding were well known in the art and routinely used by the skilled artisan. Applicants submit that the skilled molecular biologist, enlightened by the teaching of the present specification and armed with the knowledge available in the art at the time of filing of the captioned application, would be more than capable of routinely making CRCGCL polypeptides which are not 100% identical to the polypeptide of SEQ ID NO:2 encoded by a polynucleotide encompassed by the claims. In addition, the instant specification explicitly teaches for example, methods for generating an antibody against CRCGCL (*see, e.g.,*, page 27, line 1 through page 32, line 5 and page 81, line 10 through page 82, line 25). It is noted that it was well known in the art on the priority date of the present application that antibodies can be made to polypeptide fragments even though they may not be immunogenic in an animal using methods such as phage display. Armed with this disclosure, the skilled artisan could readily and routinely test whether an encoded polypeptide which is not 100% identical to the polypeptide of SEQ ID NO:2 could generate an antibody to CRCGCL.

The Examiner further contends that Applicant's argument "that the specification teaches which residues comprise the epitope bearing portions of the protein corresponding to SEQ ID NO:2 and also how to determine which amino acid changes are phenotypically silent and how to determine which amino acids of the protein are essential to its function" is not deemed persuasive "because, primarily, the specification has not disclosed what the function of the polypeptide is." (*See, e.g.,* Paper 11, Page 8, Paragraph 10.)

Applicants respectfully disagree and again point out that in order to enable the claimed invention as required by 35 U.S.C. § 112, the specification need only enable a person of ordinary skill in the art to make the claimed nucleic acids and practice a single use of the claimed nucleic acids without undue experimentation.[2] In our response to the rejection under § 101 above, Applicants have provided evidence confirming the asserted utilities of a CRCGCL polypeptide (or fragments thereof) encompassed by the claimed polynucleotides, for example, in binding a cytokine, activating the Jak-STAT signal transduction pathway, and modulating the proliferation of immune cells. Further, Applicants submit that to be fully enabled, the nucleic acid molecules of the invention do not necessarily have to encode a polypeptide having biological activity, but need merely have application in a single use, such as, for example, as a probe, or to encode a polypeptide that binds an antibody to CRCGCL polypeptide.

Applicants further disagree with Examiner's allegation that "the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make." *See, e.g.,* Paper 11, Page 8, Paragraph 10. Applicants point out that, as discussed above, the enablement requirement of 35 U.S.C. § 112 is fully satisfied if the specification enables a person skilled in the art to make the claimed polynucleotides and practice a single use of the claimed nucleic acids, such as, for example, use of polypeptides encoded by these nucleic acids to generate antibodies that specifically bind CRCGCL, without undue experimentation. As discussed above and in our response of June 2, 2000 (Paper 10), the specification discloses specific regions of CRCGCL predicted to be antigenic. The design of polynucleotides which encode a polypeptide having 95% or more identity, or having 1-30 substitutions compared to a known reference polypeptide sequence of 348 or more amino acids, but which retain at least one of the antigenic sites of the reference protein is routine in

---

[2] The Applicant need show utility for only one disclosed purpose. See *Raytheon Co. v. Roper Corp.*, 220 USPQ 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984); *Ex parte Lanham*, 121 USPQ 223 (Pat. Off. Bd. App. 1958).

the art. In addition, the specification explicitly teaches specific domains which are conserved between members of the Cytokine Receptor family (*see, e.g.,* the specification at page 7, lines 24-35), including, for example, conserved domains between CRCGCL and IL-2 receptor gamma, such as a Jak box (*see, e.g.,* the specification at page 2, lines 27-34 and Figure 2). The design of polynucleotides which encode a polypeptide having 95% or more identity, or having 1-30 substitutions compared to a known reference polypeptide sequence of 348 or more amino acids, but which retain at least one of the conserved domains of the reference protein is routine in the art. Accordingly, Applicants submit that one skilled in the art, enlightened by the disclosure and guidance of the instant application, is more than capable of making and using nucleic acids encoding polypeptides having 1-30 amino acid substitutions compared to a CRCGCL polypeptide or having 95% or more identity to CRCGCL polypeptides.

Applicants submit that because of (1) the disclosure and characterization in the specification of the nucleic acid and polypeptide sequence corresponding to CRCGCL; (2) the availability of routine techniques for generating fragments or variants to a known nucleic acid sequence, for expressing the polypeptide encoded by the fragments or variants, for generating antibodies against the polypeptide, for assaying the ability of a nucleic acid to function as a probe, for assaying the ability of an antibody to bind a polypeptide; for assaying the ability of a polypeptide to bind a cytokine; and for assaying the ability of a polypeptide to activate the Jak-STAT signal transduction pathway; (3) the high level of skill in the field of molecular biology and immunology; and (4) the direction and guidance provided by the specification, one skilled in the art could routinely generate the claimed nucleic acids and determine whether these nucleic acids encode polypeptides that bind an antibody to CRCGCL polypeptide, or bind a cytokine or activate the Jaks-STAT signal transduction pathway or modulate immune cell proliferation and/or differentiation.

A patent Applicant's specification disclosure which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d. 220, 223-224, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). Applicants submit that the Examiner has provided no evidence to doubt the enablement of the claimed CRCGCL polynucleotides.

In view of the foregoing, Applicants submit that the claims fully meet the enablement requirements of Section 112, first paragraph, and respectfully request that the rejection be withdrawn.

V. Miscellaneous

Applicants have added claims 140-151 which are similar in scope to claims 51-59 that were canceled by Applicant's amendment of June 12, 2000 (*see, e.g.,* Paper 10). Applicants submit that the new claims encompass polynucleotides which have credible, substantial and specific utility, for example, to bind a cytokine, and inhibit the action of CRCGCL. The Declaration Under § 1.132 of Paul A. Moore submitted herewith, confirms these asserted utilities by providing experimental evidence that a fragment of CRCGCL alone binds a cytokine and inhibits the activity of CRCGCL in activating the Jak-STAT pathway.

Conclusion

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: 2/27/01

Michele M. Wales (Reg. No. 43,975)
Attorney for Applicants

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850
Telephone: (301) 610-5772

MMW/CB